

REMARKS/ARGUMENTS

Original Claim 7 has been canceled. Claims 1-6 have been amended in a non-limiting manner to improve readability. Descriptive support for new Claims 8-10 is found in Examples 5 (1.5 equiv.) and 6 (1.1 equiv.) on pages 6-7 of the Specification. Descriptive support for new Claim 11 is found in Example 2 on page 5 of the Specification. Descriptive support for new Claim 12 is found in Examples 1 and 3-6 on pages 4-7 of the Specification. No new matter is presented in this amendment.

1. Applicant's claim for priority under 35 U.S.C. §119 should be granted

The Examiner acknowledged Applicant's claim for priority under 35 U.S.C. §119 of the August 27, 2002, filing date of Czech Republic Application No. PV 2002-2906 (Office Action (OA), dated April 25, 2008, p. 2, para. 1). However, because an English translation of the priority papers filed in PCT/CZ2003/00049 had not been filed of record in this application and the Examiner cited and applied intervening art against the claims in the Office Action dated April 25, 2008, the Examiner concluded that Applicant's claim for priority under 35 U.S.C. §119 had not been perfected and granted Applicant a filing date of August 28, 2003, the filing date of their §371 international application.

To perfect Applicant's claim for priority under 35 U.S.C. §119 and credit this application with benefit of the August 27, 2002, filing date of Czech Republic Application No. PV 2002-2906, Applicant submits herewith a photocopy of the certified copy of Czech Republic Application No. PV 2002-2906 filed with the international receiving office on August 27, 2003, for PCT/CZ03/00049 and a certified English translation thereof. In accordance with 37 CFR §1.55(a)(4)(ii), Applicant also states that the English translation of Czech Republic Application No. PV 2002-2906 filed with this reply is accurate. It should be apparent from the English translation of Czech Republic Application No. PV 2002-2906 submitted herewith that the foreign application describes and claims the subject matter

Applicant describes and claims in the present application and that Applicant should be accorded benefit under 35 U.S.C. §119 of the August 27, 2002, filing date thereof.

2. The rejection of Claims 1-6 under 35 U.S.C. §103 should be withdrawn

A. Mukarram is not prior art to the subject matter claimed

Mukarram (WO 2005/012300, published February 10, 2005 (filed August 4, 2003); U.S Patent 7,291,735, issued November 6, 2007 (PCT filed August 4, 2003)) is not prior art to the subject matter Applicants presently claim. Having perfected its claim for priority under 35 U.S.C. §119, Applicant has established that it is entitled to benefit of the August 27, 2002, filing date of Czech Republic Application No. PV 2002-2906. Mukarram's earliest filing date is later than Applicant's priority filing date of August 27, 2002. Accordingly, Applicants respectfully request that the Examiner withdraw the outstanding rejection of Claims 1-6 under 35 U.S.C. §103 in view of Badore (Badore et al., U.S. Patent 4,847,265, issued July 11, 1989) or Bousquet (Bousquet et al., U.S. 6,429,210 B1, issued August 6, 2002) in view of Lifshitz-Liron (Lifshitz et al., U.S. Patent 7,074,928 B2, issued July 11, 2006) "supplemented with Mukarram (WO 2005/012300, published February 10, 2005 (filed August 4, 2003); U.S Patent 7,291,735, issued November 6, 2007 (PCT filed August 4, 2003)).

B. Claims 1-6 are patentable over Bardore or Bousquet in view of Lifshitz

The Examiner finds that Badore and Bousquet would have taught a person having ordinary skill in the art to separate clopidogrel hydrogen sulphate in crystalline Form I (melting point 184°C./184±3°C.) from a solution of clopidogrel hydrogen sulphate in an acetone solvent. The Examiner points to Badore, col. 6, example 1(e), ll. 47-64, and Bousquet, col. 9, example 1B, ll. 44-60 (OA, p. 3, "scope and content of the prior art").

The Examiner finds that Lifshitz would have taught a person having ordinary skill in the art that "variation of solvent such as ether may be employed to obtain the same product"

(OA, p. 3, “difference between prior art and claims”; emphasis added). The Examiner points to Lifshitz, cols. 19-20, examples of Form I, in support of her finding. Applicants understand that Lifshitz’ Examples 18-25 (Lifshitz, cols. 20-21) relate to the separation of Form I from various solutions. However, but for her statement that a “solvent such as ether may be employed”, the Examiner has not discussed any of Lifshitz’ examples or teachings relating specifically to the separation of Form I from solutions. Consistent with the Examiner’s general description of Lifschitz’ examples relating to Form I at or about columns 19-20, Examples 18-25 appear to describe the separation of Form I out of a solution of clopidogrel in the form of a free base or salt in a solvent comprising a significant amount of methyl t-butyl ether or diethylether.

Without expressly determining the full scope and content of the subject matter Applicant claims, the Examiner nevertheless proceeds to find that “[t]he difference between the instant claims and the prior art process is that instead of acetone, the instant claims employed alcohol, esters, or mixture thereof” (OA, p. 3, “the difference between the prior art and the claims”). Applicant presumes from the finding that the Examiner concluded that the solvent of the solutions from which Form I is separated in accordance with Applicant’s claim language is a solvent selected from the group consisting of a primary, secondary and tertiary C1-C5 alcohol, an ester of a primary, secondary and tertiary C1-C5 alcohol with a C1-C4 carboxylic acid, and mixtures thereof. Applicant also presumes from the Examiner’s finding that the solvent of the solutions from which Form I was separated in accordance with the teachings of the prior art relied upon to establish obviousness is not a solvent selected from the group consisting of a primary, secondary and tertiary C1-C5 alcohol, an ester of a primary, secondary and tertiary C1-C5 alcohol with a C1-C4 carboxylic acid, and mixtures thereof. Rather, the Examiner appears to have found that the prior art solvents described by Badore, Bousquet, and Lifshitz are selected from the group of solvents consisting of acetone,

methyl t-butylether, and diethylether, because Mukarram, which Applicant now has overcome by perfecting its claim for priority under 35 U.S.C. §119, alone is relied upon by the Examiner for its teaching and/or suggestion to use a solvent of the class Applicant used to separate Form I from solution.

Hence, without Mukarram's disclosure, the Examiner is hard-pressed to find support in the prior art for anything more than "obvious to try" as the incentive, motivation, or suggestion for a person having ordinary skill in the art to separate Form I from a solution of clopidogrel in the form of the free base or salt in a solvent selected from the group consisting of C1-C5 alcohols, esters of C1-C5 alcohols with C1-C4 carboxylic acids, and mixtures thereof. One must be motivated to do more than try each of numerous possible choices until one possibly succeeds, especially where the prior art provides a person having ordinary skill in the art with no guidance or direction towards those choices likely to succeed. *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006).

Nevertheless, the Examiner finds, based on the teachings of the applied prior art considered in combination, that persons having ordinary skill in the art would have understood that Form I may be separated from a solution of clopidogrel in the form of the free base or salt in any and all of the various solvents known in the art. The Examiner states (OA, p. 3, "prima facie obviousness - rational [sic] and motivation"):

One having ordinary skill in the art would be motivated to employ variation of solvents in obtaining the same product because one has been suggested that similar organic solvent would give the same product as evidenced by the per ponderous (sic) of references . . . that changing solvents is a routine choice by a person having ordinary skill and lower alkanoyl-lower alcohol esters are common laboratory solvents.

Applicant disagrees.

First, the Examiner appears to recognize that C1-C5 alcohols and esters of C1-C5 alcohols and C1-C4 carboxylic acids are not disclosed, taught, and/or reasonably suggested by any one of the prior art references applied against the claims (Mukarram is not prior art) as

a solvent from which Form I may be separated out of a solution of clopidogrel in the form of a free base or salt. The Examiner finds that acetone and ethers are prior art solvents from which Badore, Bousquet, and Lifshitz separate Form I.

Second, Lifshitz appears to teach that crystalline Form I may be obtained from a suspension of the amorphous form of clopidogrel hydrogen sulphate or the free base in an ether (Lifshitz, col. 7, l. 50, to col. 8, l. 10). Lifshitz appears to teach that amorphous and other crystalline forms of clopidogrel hydrogen sulphate may be obtained from solutions of clopidogrel hydrogen sulphate or its free base in other solvents under particular conditions and techniques most often employing an antisolvent (Lifshitz, col. 4, l. 66, to col. 5, l. 67; Lifshitz, col. 6, ll. 1-55; Lifshitz, col. 8, ll. 11-63; Lifshitz, col. 6, l. 65, to col. 7, l. 30; Lifshitz, col. 7, ll. 30-49; and Lifshitz, col. 8, l. 64, to col. 10, l. 36). Lifshitz teaches (Lifshitz, col. 11, ll. 31-35; emphasis added):

The new crystalline forms of clopidogrel hydrogen sulphate are solvates of various solvents. Clopidogrel hydrogensulfate Form III is a solvate of 1-butanol. Form IV is considered a solvate of isopropanol. Form V is a solvate of 2-butanol. Form VI is a solvate of 1-propanol.

Regarding the formation of crystalline Form II, Lifshitz instructs (Lifshitz, col. 10, ll. 37-50; emphasis added):

The present invention further provides a process for preparing clopidogrel hydrogensulfate Form II comprising the steps of preparing a solution of clopidogrel hydrogensulfate in a solvent selected from the group consisting of chloroform, dichloromethane, 1,4-dioxane, toluene, ethyl acetate, methylethyl ketone, and t-butylmethyl ether, precipitating clopidogrel hydrogensulfate from the solution, and separating the clopidogrel hydrogensulfate.

As the examples illustrate, one skilled in the art would appreciate that the optimal conditions for crystallizing clopidogrel hydrogensulfate Form II from these solvents is solvent dependent. The conditions used for crystallization may vary from one solvent to another.

Applicant suggests that persons having ordinary skill in the art having the combined teachings of Badore, Bousquet, and Lifshitz before them, reasonably would not have expected, as the Examiner finds, that “similar organic solvent[s] would give the same

product” (OA, p. 3, “prima facie obviousness - rational[e] and motivation”). The prior art the Examiner cites in support of her conclusion that the subject matter Applicant claims rejects the Examiner’s finding as clearly erroneous. Rather, the evidence shows the Examiner erred in rejecting Applicant’s claimed methods under 35 U.S.C. §103 for obviousness in view of overwhelming prior art evidence to the contrary.

References must be read for everything they would have fairly taught a person having ordinary skill in the art. *In re Lamberti*, 545 F.2d 747, 750 ((CCPA 1976). Evidence which supports patentability should be considered with the evidence which negates patentability. *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988).

3. Rejection of Claims 1-6 under 35 U.S.C. §112, 1st para., should be withdrawn

In support of the rejection of Applicant’s Claims 1-6 under 35 U.S.C. § 112, 1st para., for noncompliance with its enablement requirement, the Examiner cites an August 16, 2002 publication of Kirk-Othmer Encyclopedia of Chemical Technology, pp. 95-147, which generally relates to processes of making polymorphic forms of compounds, to establish the compound specific and highly unpredictable nature of the art (OA, pp. 3-4, bridging para.). Applicant does not deny the Examiner’s finding that the art is generally unpredictable and compound specific. Lifshitz’ teaching that production of the crystalline forms of clopidogrel hydrogen sulphate is dependent on the specific solvent from which a particular form of clopidogrel hydrogen sulphate is separated and the crystallization conditions is consistent with Kirk-Othmer’s teaching. In that light, Applicant expects the Examiner to withdraw first the rejection of its claimed method under 35 U.S.C. §103 over the combined prior art teachings.

In the Examiner’s rejection of Applicant’s claimed method under 35 U.S.C. §112, 1st para., the Examiner states (OA, p. 3; emphasis added):

The Mukarram [(‘300)] . . . reference provided evidence that the instant claimed process is inoperable in producing form I exclusively (see ‘300 p.3 paragraphs after structural formula). Specifically, Mukarram ‘300 disclosed that form I without contamination of other forms would have a higher melting point between 198-200°C. All the examples made from the instantly claimed process being evidence in the specification have melting points of 184-186°C, thus, are inoperable for making exclusively form I.

First, the Examiner erred in concluding that Applicant’s claims are directed to a method of “producing form I exclusively”(emphasis added). *Id.* The method Applicant claims produces Form I by separating clopidogrel hydrogen sulphate out of a solution of clopidogrel in the form of the free base or salt in an alcohol or ester solvent. The Specification teaches (Spec., p. 3, first para.; emphasis added):

It has now been found out that if clopidogrel hydrogen sulphate is allowed to crystallise (sic) by the procedure according to this invention, Form I having a high and defined content can be obtained in a reproducible way.

The Specification also teaches that the detection of Form II is reliably low when employing Applicant’s method for manufacturing Form I (Spec., p. 4, ll. 14-16). Applicant’s Examples 1-6 report results consistent with the Specification’s teachings.

Second, Applicant’s Specification documents the quality of the Form I produced by the claimed method by X-ray diffractogram (XRD)(Figures 1, 4, and 5), Fourier Transformation infrared spectroscopy (FTIR)(Figure 2), and differential calorimetry (DSC)(Figure 3)(Spec., pp. 3-4, bridging para.; pp. 4-7, Examples 1-6, and Figures 1-5), in addition to a melting points of 185-187°C. (Spec., pp. 4-5, Example 1) and 184-186°C. (Spec., pp.5-6, Examples 2-4).

Consistent with Applicant’s disclosure, Badore (first filed February 12, 1988) and Bousquet (first filed June 10, 1999) describe production of Form I having a melting point of $184\pm 3^{\circ}\text{C}$. (Badore, Example 1(e); Bousquet, Examples 1B and 1C). Badore established the production and purity of Form I by NMR spectroscopy and high pressure liquid chromatography (Badore, cols. 4-5). Bousquet identified crystalline Form I by IR (Bousquet,

Figure 4) and XRD (Bousquet, Figure 1). Applicant confirmed production and purity of crystalline Form I by IR (Figure 2), XRD (Figures 1, 4, and 5), and differential calorimetry (DSC)(Figure 3). A comparison of Bousquet's infrared spectrum and X-ray diffractogram for crystalline Form I to Applicant's infrared spectrum and X-ray diffractograms for crystalline Form I shows no significant differences. Moreover, the reported melting points are substantially the same ($184\pm 3^{\circ}\text{C}$).

In its only example, Mukarram '300 teaches that (+)-(S)-Clopidogrel bisulfate Form I was obtained in 99.96% purity from an ethyl acetate solution of (+)-(S)-Clopidogrel after seeding with (+)-(S)-Clopidogrel bisulfate Form I, adding concentrated sulfuric acid, refluxing for 1 hour, filtering the product, washing with ethyl acetate, and drying at 60 to 70°C for 6-8 hours (Mukarram '300, p. 5, Example (b)). The non-prior art reference teaches (Mukarram '300, p. 3, last sentence, and p. 5, last sentence), "The Form I of (+)-(S)-Clopidogrel bisulfate has been confirmed on the basis of IR, XRD and melting point." Mukarram '300 reports the IR, XRD, and melting point data for Form I in its only Table (Mukarram '300, p. 4, Table).

Mukarram '300 acknowledges (Mukarram '300, p. 3, second para.):

The Form I of Clopidogrel bisulfate is well characterized by IR and XRD. These values are identical with the reported values of Form I (reported in US patent 6,429,210 B1 [Bousquet]). HPLC purity of Clopidogrel bisulfate Form-I prepared using ethyl acetate solvent is found more than 99%. An increase in melting point is observed in our process, i.e., $198-200^{\circ}\text{C}$ in comparison to 181.2°C disclosed in US patent 6,429,210 B1. The increase in melting point indicates higher purity of Form-I from what is reported in the "210" patent.

Applicant notes that the data reported in the Table on page 4 of Mukarram '300 is not supported by an infrared spectrum or X-ray diffractogram. Mukarram's statements that "Form I of (+)-(S)-Clopidogrel bisulfate has been confirmed on the basis of IR, XRD and melting point" is not supported by any objective evidence. Bousquet's IR and XRD data are confirmed by infrared spectrum or X-ray diffractogram and acknowledged by Mukarram to

be identical to the IR and XRD data reported in its Table. Mukarram '300 also erroneously reports that Bousquet disclosed a melting point of 181.2°C for Form I. Bousquet disclosed a melting point of 184±3°C for Form I (Bousquet, cols. 9-10, Examples 1B and 1C.).

Applicant is confused, and the Examiner should be confused, how the IR and X-ray diffraction data reported by Bousquet for Form I can be "identical" to the IR and X-ray diffraction data reported by Mukarram '300 for Form I if the measured melting points reported for Form I differ by more than 11°C. Moreover, persons having ordinary skill in the art likely would expect Bousquet to have reported more than 184±3°C error for its reported melting point for Form I if, as Mukarram '300 reports, the melting point for 99.96% pure Form I is 198-200°C., especially since Bousquet and Mukarram '300 both report melting points of 176±3°C (Bousquet, col. 10, Examples 2 and 3) and 176-178°C. (Mukarram '300, p. 4, Table) for crystalline Form II.

Furthermore, Mukarram '300 appears to have had prior knowledge of Lifshitz's disclosure regarding processes for manufacturing crystalline Forms I, II, III, IV, and V and amorphous forms of clopidogrel hydrogen sulfate using different combinations of alcohol and ether (Mukarram '300, p. 2, second para.). Accordingly, persons having ordinary skill in the art would have known Lipshitz' report that clopidogrel hydrogen sulfate can form solvates in various solvents which are new crystalline forms, e.g., with alcohols (Lipshitz, col. 11, ll. 26-40). Applicant respectfully suggests that persons having ordinary skill in the art would have recognized that Mukarram's use of ethyl acetate as a solvent in its process for preparing crystalline Form I of clopidogrel hydrogen sulfate, under the conditions reported in its one example, may have been susceptible to formation of a solvate with a melting point higher than that of Form I.

In short, the Examiner has the initial burden of proof to support a rejection of Applicant's claims under 35 U.S.C. § 112, first paragraph, for inoperability and/or

nonenablement. Where, as here, the Specification contains a teaching of the manner and process of making and using the invention in terms corresponding in scope with those of the claims, the disclosure must be taken as in compliance with the enablement requirement of the first paragraph of 35 U.S.C. § 112 unless there is reason to doubt the objective truth of statements relied on for enablement. *In re Marzocchi*, 439 F.2d 220, 223-224 (CCPA 1971).

[I]t is incumbent upon [one alleging that a disclosure is nonenabling] . . . to explain why it doubts the truth or accuracy of any statement in the supporting disclosure and to back up assertions of its own with acceptable evidence and reasoning

Similarly, the examiner's doubts as to operability of the claimed invention must be reasonably supported by the evidence of record. *In re Fouche*, 439 F.2d 1237, 1242-1243 (CCPA 1971). Applicant may remove the examiner's doubt as to the operability of its claimed invention by suitable proofs. *In re Marzocchi*, 439 F.2d at 223.

Ultimately, when determining patentability of the claimed invention, the examiner must weigh all the evidence favoring patentability against all the countervailing evidence. *In re Piasecki*, 745 F.2d 1468, 1471-1472 (Fed. Cir. 1984); *In re Skoll*, 523 F.2d 1392, 1397 (CCPA 1975). Here, the Examiner points to one example in Mukarram '300 and a Table indicating that crystalline Form I has a different melting point from that reported in at least four of Applicant's examples as the only evidence which would have led a person having ordinary skill in the art to suspect Applicant did not separate Form I. To the contrary, however, Badore's melting point for Form I, first reported in 1987, and Bousquet's melting point for Form I, first reported more than ten years later, both agree with the melting point Applicant's Specification first described in 2002. Bousquet's IR and X-ray diffraction data agree with Applicant's IR and X-ray diffraction data. Mukarram concedes that Bousquet's IR and X-ray diffraction data and Applicant's IR and X-ray diffraction data confirm the separation of Form I. Mukarram's explanation for the different melting point it reported

appears to be incredible. Moreover, Lifshitz provides a reasonable explanation for Mukarram's discrepancy.

In short, the overwhelming weight of the evidence of record indicates that the process Applicant claims is operable as described in Applicant's supporting Specification and confirmed by melting points consistent with all the prior art disclosures, IR data consistent with all the prior art disclosures and Mukarram's subsequent disclosure, and X-ray diffraction data consistent with all the prior art disclosures and Mukarram's subsequent disclosure. In fact, Mukarram concedes that two-thirds of the evidence it relied upon to establish that he separated Form I is identical to that reported by Badore, Bousquet, and Applicant. Applicant submits that the Examiner's conclusion of inoperability is against the greater weight of the evidence of record and should be withdrawn

Finally, Applicant has perfected its claim for priority under 35 U.S.C. §119. Thus, Mukarram is not prior art with respect to the subject matter Applicant claims. Extrinsic evidence, including non-prior art disclosures, may be considered to explain what the prior art teachings would have meant to persons having ordinary skill in the art at the time Applicant's application was filed. *In re Baxter Travenol Labs.*, 952 F.2d 388, 390 (Fed. Cir. 1991). Again, Mukarram is not prior art. Here, the Examiner has not explained why persons having ordinary skill in the art would have doubted the conventional teachings of Badore and Bousquet. Moreover, the Examiner has not explained why persons having ordinary skill in the art would have doubted the teachings in Applicant's Specification which are consistent with all the conventional prior art teachings. The Examiner's rejection denies years of knowledge and skill in the art based on one inconsistent measurement in one non-prior art example which would not have been available to persons having ordinary skill in the art on August 27, 2002, the date to which Applicant claim priority under 35 U.S.C. §119.

CONCLUSION

For the reasons given herein, it is respectfully submitted that the Examiner's rejections under 35 U.S.C. §103 and 35 U.S.C. §112, first paragraph, should be withdrawn and allowable Claims 1-6 of this application should be passed to issue.

Respectfully submitted,

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A handwritten signature in black ink, appearing to read 'R. Treanor', is written over a horizontal line.

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